# Fever of Unknown Origin

Garret Pachtinger, VMD, and Lesley G. King, MVB, Diplomate ACVECC, ACVIM, & ECVIM (Companion Animal), University of Pennsylvania

## PROFILE

### Definition

Elevations in body temperature are caused by hyperthermia or fever. Hyperthermia occurs when an elevated rectal temperature is associated with increased intrinsic heat production and/or increased ambient temperature, accompanied by the inability to dissipate heat. In hyperthermic animals, the hypothalamic temperature set point is normal. In contrast, in animals with fever the hypothalamic set point is elevated, typically by infection, inflammation, neoplasia, or drug administration. The underlying cause of fever is usually—but not always—easily explained.

In human medicine, fever of unknown origin (FUO) is defined as an illness of more than 3-weeks' duration with a temperature higher than 101° F (38.4° C) on several occasions after 1 week of hospitalization and evaluation. While there is no accepted definition in veterinary patients, FUO is considered to be present when an obvious cause for a persistent fever has not been found after routine examination and diagnostic tests.

**Systems.** Disease in almost any body system can cause a fever, and signs vary depending on the body system affected.

**Geographic Distribution.** May be important for certain infectious or tick-borne causes of fever.

### Signalment

**Breed Predilection.** Certain diseases have breed associations (eg, shar-pei fever, hypertrophic osteodystrophy in weimaraners).

**Age & Range.** Any age, depending on cause. Age may direct differential diagnoses (eg, neoplasia may be more likely in an older patient).

### Causes

The **Table** outlines possible causes of fever. Geographic region and caseload (primary practice versus a referral facility) are important with regard to underlying causes.

### Risk Factors

Incomplete or absent vaccination, lack of preventive medications (ie, heartworm, flea/tick), drug exposure, habitation in areas enzootic for specific diseases.

**POSSIBLE CAUSES OF FEVER**

| | |
|---|---|
| **Infectious** | |
| Bacterial | Abscess, anaplasmosis, cholangiohepatitis, bartonellosis, brucellosis, endocarditis, hemobartonellosis, leptospirosis, Lyme disease, meningitis, mycoplasmosis osteomyelitis, peritonitis, pneumonia, prostatitis, pyometra, pyothorax, septic arthritis, urinary disorders |
| Viral | Canine distemper, FeLV, FIV, FIP |
| Rickettsial | Ehrlichiosis, Rocky Mountain spotted fever |
| Fungal | Blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis |
| Protozoal | Babesiosis, hepatozoonosis, neosporosis, toxoplasmosis |
| Parasitic | Heartworm, whipworm |
| **Immune-mediated** | Hypereosinophilic syndrome, immune-mediated hemolytic anemia or thrombocytopenia, immune-mediated polyarthritis, nodular panniculitis, rheumatoid arthritis, steroid-responsive meningitis, systemic lupus erythematosus |
| **Inflammatory** | Hypertrophic osteodystrophy, pancreatitis, panosteitis, pansteatitis |
| **Neoplasia** | |
| Hematopoietic | Leukemia, lymphoma, malignant histiocytosis, myeloma |
| Solid tumors | Gastric, hepatic, necrotic, others |
| **Miscellaneous** | Allergic reactions, drug reactions (tetracycline, trimethoprim sulfa, itraconazole, cimetidine), shar-pei fever, toxins (arsenic, ricin) |

FeLV = feline leukemia virus; FIP = feline infectious peritonitis; FIV = feline immunodeficiency virus


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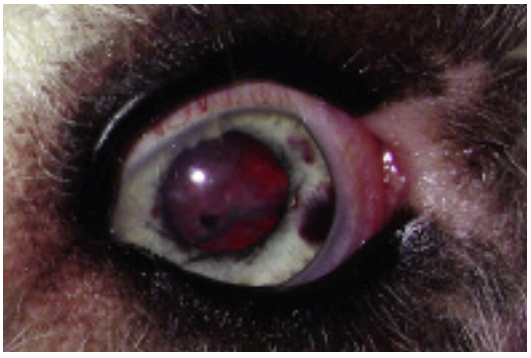
### Pathophysiology

Fever is caused by an increased thermoregulatory set point. The anterior preoptic area of the hypothalamus contains specialized neurons that control thermoregulation, maintaining body temperature at a "normal" set point. Fever occurs when the hypothalamus "resets" to a higher point as a result of the action of exogenous or endogenous pyrogens.

### Signs

**History.** Historical information should include:

- Signalment/clinical signs
- Vaccination status
- Deworming & heartworm prevention history
- Exposure to infectious agents
- Travel history
- Recent drug administration
- Recent veterinary visits, including previous diagnoses and response to therapy
- Complete medical & surgical history.



1 In addition to iridial hemorrhage, retinal hemorrhage was evident in the fundus of this 6-year-old spayed female mixed-breed dog. CBC showed significant thrombocytopenia. A complete workup was performed and the patient was diagnosed with immune-mediated thrombocytopenia.

**Physical Examination.** Should be thorough, systematic, and repeated at least twice daily to look for changes (eg, development of heart murmur, masses). Special care should be taken to assess:

- Lymphadenopathy
- Cranial organomegaly (liver, spleen)
- Cardiac auscultation (murmur, arrhythmia)
- Petechiae or ecchymosis
- Neck or back pain
- Disease in the oral cavity (teeth, oral ulceration)
- Joint pain or effusion
- Fundic (retinal) examination (**Figure 1**).

### Pain Index

General malaise related to the fever; variable pain related to the underlying cause of fever (eg, joint pain in polyarthritis)

## DIAGNOSIS

### Definitive Diagnosis

The long list of potential causes of FUO mandates a thorough workup (**Figure 2**).

### Differential Diagnosis

Hyperthermia (nonpyrogenic): possible causes include recent exercise, seizures, high ambient temperatures, upper airway obstruction, hyperthyroidism, pheochromocytoma, and drugs/medications

### Laboratory Findings/Imaging

- **CBC (and blood smear)**—Routine hematology evaluating red blood cell count and morphology, platelet count, white blood cell count and morphology, and the presence of infectious organisms
- **Biochemistry**—A complete serum biochemical profile assessing organ function and electrolyte imbalances
- **Coagulation testing**—Indicates possible petechiae/ecchymosis, thrombocytopenia, and disseminated intravascular coagulation; should be performed before fine-needle aspiration
- **Blood culture**—Aerobic and anaerobic, may need serial cultures
- **Urinalysis, sediment evaluation, urine culture & sensitivity**—Unless contraindicated, cystocentesis or a sample obtained by catheterization; analysis should focus on the presence of white blood cells, bacteria, crystalluria, and proteinuria
- **Infectious disease titers**—Species- and history-dependent (eg, FeLV, heartworms and ticks in dogs)
- **Fecal parasitology & microbiology**—Evaluation of parasites, ova, occult blood, or abnormal bacteria
- **Radiographs**—Thoracic and abdominal radiographs identify septic, inflammatory, or neoplastic processes; orthopedic radiographs should be considered
- **Abdominal ultrasonography**—Further evaluation of abdominal cavity to detect, for example, effusions, masses, stump pyometra, prostatitis

FeLV = feline leukemia virus; FUO = fever of unknown origin

- **Echocardiography**—Further evaluation of cardiac disease, rule out endocarditis
- **Fine-needle aspiration/biopsy**—Samples for cytology and culture to evaluate, for example, swellings, organomegaly, lymphadenopathy
- **Bone marrow aspiration**—If there are CBC changes suggestive of bone marrow disease
- **Joint/synovial fluid analysis**—If lameness, joint swelling, heat, or discomfort is present
- **Cerebrospinal fluid analysis**—If neurologic deficits or neck pain is present
- **Advanced imaging**—Computed tomography, magnetic resonance imaging

## TREATMENT

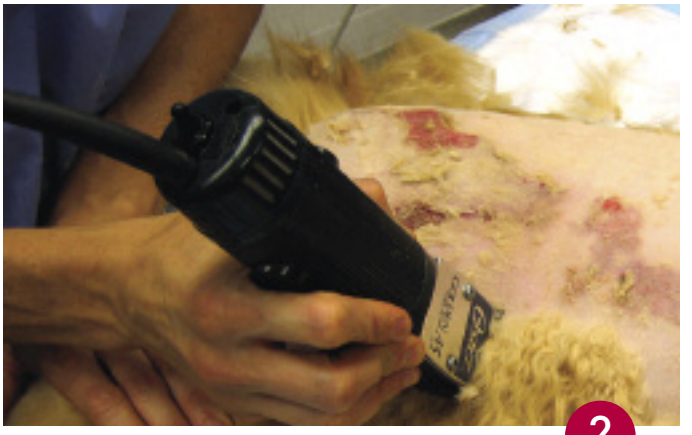
When no diagnosis is made (eg, exhaustive tests do not yield a diagnosis or the owner has financial limitations), a therapeutic trial may be undertaken after careful consideration of risks and benefits (eg, a decision to use corticosteroids without ruling out an infectious cause).

### Inpatient or Outpatient

Animals with fever high enough to cause malaise, anorexia, and dehydration require hospitalization for supportive care. Temperatures greater than 106° F (41.1° C) can cause electrolyte disturbances, organ damage, disseminated intravascular coagulation, and even death, and these animals require aggressive in-hospital therapy.

### Medical

- Treatment of severe hyperthermia involves rapid external cooling, including convective heat loss (spray patient with water and place in front of fan), conduction (place on cool surface, administer chilled intravenous fluids, and place ice packs in axillary and inguinal regions), and evaporative heat loss (wet footpads with alcohol).
- In animals with true fever, the hypothalmic set point is reset and external cooling can be relatively ineffective because the body attempts to maintain the new temperature. True fever may require treatment with agents that reset the hypothalamic thermoregulatory set point.
- Antipyretic agents include salicylates, acetaminophen, dipyrone, and flunixin meglumine, all of which inhibit prostaglandin synthesis. Phenothiazines, such as acepromazine, peripherally block dopamine and adrenergic receptors, resulting in vasodilation. Intravenous fluids may help decrease temperature and improve hydration status.



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This 8-year-old castrated male domestic shorthair presented for vague clinical signs, including fever, decreased appetite, and lethargy. Careful physical examination revealed a significant dermatologic abnormality with skin sloughing. Skin biopsy confirmed an immune-mediated vasculitis.

### Nutritional Aspects

Prolonged decreases in caloric intake or complete anorexia due to persistent fever may require placement of a feeding tube or administration of parenteral nutrition.

### Client Education

A thorough and potentially costly diagnostic workup may be needed to properly evaluate FUO.

## MEDICATIONS

### Specific vs Supportive

Appropriate therapy is dictated by the specific underlying cause of fever. If a cause cannot be found and/or test results are pending, supportive care and measures to address clinical signs include:

- **Intravenous fluids** to improve hydration and reduce temperature
- A **penicillin or cephalosporin with an aminoglycoside or quinolone** (reasonable choice for initial empirical treatment of suspected bacterial infections)
- **Doxycycline** for suspected rickettsial or spirochete infections
- **Clindamycin or a sulfa-based antibiotic** for suspected toxoplasmosis or neosporosis
- Consideration of **corticosteroids** if infection

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is ruled out and immune-mediated disease is possible
- **Chemotherapy or surgery** to treat neoplasms
- Consideration of **nonsteroidal antiinflammatory drugs** for symptomatic treatment of fever, but negative side effects (gastric, renal) must be remembered and NSAIDs should not be administered concurrently with corticosteroids (see **Steroid Therapy**, page 80).

### Precautions
Medical therapy must be carefully selected to reduce the risk for exacerbating undiagnosed disease, inducing drug toxicity or medication side effects, promoting antibiotic resistance, and interfering with further diagnostic tests.

FUO = fever of unknown origin; NSAID = nonsteroidal antiinflammatory drug; PCR = polymerase chain reaction

## FOLLOW-UP

### Prevention
Yearly veterinary evaluation, vaccination, infectious disease prophylaxis (heartworm medication, flea and tick prevention), dental care

### Complications
- Empirical therapy (eg, use of corticosteroids in animals with infectious disease)
- Fever may cause anorexia and reduced nutritional intake.
- Prolonged and severe fever can be associated with disseminated intravascular coagulation.

### At-Home Treatment
Monitor temperature and keep a log to assess response.

### Future Follow-Up
Fever may wax and wane despite supportive care until definitive therapy is implemented.

## IN GENERAL

### Relative Cost
Management of FUO may be costly due to need for hospitalization, supportive therapy, and testing. $$$$$

**Cost Key**

| | |
|---|---|
| $ = < $100 | $$$$ = $500–$1000 |
| $$ = $100–$250 | $$$$$ = > $1000 |
| $$$ = $250–$500 | |

### Future Considerations
In the future, advanced testing methodology will allow more rapid and extensive diagnosis. For example, PCR testing was once considered esoteric, but is now the standard of care for diagnosis of many infectious diseases.

See Aids & Resources, back page, for references and suggested reading.

## Our Authors CONTINUED FROM PAGE 22

**SHERRY LYNN SANDERSON**, DVM, PhD, Diplomate ACVIM & ACVN, is an associate professor at University of Georgia College of Veterinary Medicine. Her research interests include the use of nutritional management for prevention and treatment of diseases in dogs and cats. Areas of particular interest include urology and nephrology, obesity, prebiotics and probiotics, and the interaction of carnitine and taurine in canine dilated cardiomyopathy. Dr. Sanderson received her DVM from University of Minnesota. After completing a 1-year rotating internship in small animal medicine and surgery at Oklahoma State University College of Veterinary Medicine, she returned to University of Minnesota for a combined graduate program and dual residency in small animal internal medicine and small animal clinical nutrition.

**MICHAEL SCHAER**, DVM, Diplomate ACVIM & ACVECC, is professor of medicine in the department of small animal clinical sciences at University of Florida College of Veterinary Medicine. He heads the small animal medical service and is associate chief of staff of the university's small animal hospital. Dr. Schaer has served on various committees for ACVIM, ACVECC, and the University of Florida; is widely published; and lectures frequently. He received his DVM from University of Illinois and completed an internship and residency at The Animal Medical Center in New York City.

**MARGIE SCHERK**, DVM, Diplomate ABVP (Feline Practice), is a private practitioner who founded Cats Only Veterinary Clinic in Vancouver, British Columbia. Dr. Scherk has a special interest in alleviation of pain in companion animals. She has collaborated and coauthored a number of articles and wrote a chapter for the 2005 edition of Ettinger and Feldman's *Textbook of Veterinary Internal Medicine* as well as several other chapters in other texts. Dr. Scherk is past president of the American Association of Feline Practitioners, editor of the *Journal of Feline Medicine and Surgery,* and a consultant for the Veterinary Information Network's feline medicine folder. She received her DVM from University of Guelph's Ontario Veterinary College.